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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,295	10/15/2001	Avi Ashkenazi	GNE.2630P1C11	6495

35489 7590 12/07/2005

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/978,295	**Applicant(s)** ASHKENAZI ET AL.	
	Examiner Elizabeth C. Kemmerer, Ph.D.	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *58-62*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

Continuation of 13. Other: It was discovered that several references used in previous Office Actions as well as the current advisory action were not properly cited using 892 forms. Please see attached 892 form and references which complete the record.

ATTACHMENT TO THE ADVISORY ACTION

Claims 58-62 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 58-62 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The rejections are maintained for reasons of record. Applicant's arguments (submitted in the after-final response received 28 October 2005) have been fully considered but are not found to be persuasive for the following reasons. Most of the arguments have been previously made on the record, and are not found to be persuasive for the reasons of record. However, several new arguments and evidence in the form of publications have been submitted. These will be addressed below.

Applicant points to Pitti et al. and Bieche et al. as evidence that those skilled in the art used the same control as the one used in the application. However, both Pitti et al. and Bieche et al. did not rely solely upon the PCR assay using a control from blood genomic DNA to make conclusions. Pitti et al. also looked at northern blot analysis, ligand binding analysis, apoptosis induction analysis, and *in situ* hybridization analysis. Pitti et al. also ran an additional control in the PCR assays, using flanking DNA regions in tumor samples compared to blood DNA samples (p. 701, paragraph bridging the two columns). Bieche et al. relied upon Southern blotting to confirm the PCR results and

note that not all samples showing PCR amplification also showed amplification by Southern blotting (p. 664, last paragraph before Discussion section). This was especially true for sequences that were amplified at low levels comparable to the levels that instant PRO351 was shown to be amplified. Finally, it is noted that publications have been cited as evidence that matched, cancer-free tissue samples are used as controls. See, for example, Hu et al. and Chen et al.

Applicant criticizes Hittelman et al. support the asserted utility in that Hittelman et al. state that gene amplification would lead to diagnosis of a cancerous or pre-cancerous state. This is not found to be persuasive because the specification does not assert that a positive result in the gene amplification assay indicates that the PRO clone assayed is useful as a diagnostic tool for *pre-cancerous* tissue. Rather, the specification indicates that a positive result in the assay indicates that the PRO clone can be used in the diagnostic determination of the *presence* of cancers. Hittelman et al. provide evidence that a positive result can also correlate with damaged, but not cancerous, lung epithelium. Thus, further research would be required to reasonably confirm whether any particular PRO clone could be used as a diagnostic tool for cancer.

Applicant criticizes the Lian et al. publication by characterizing Lian et al. as being limited to differentiating myeloid cells and not to genes in general. Applicant also argues that Lian et al. use a very insensitive method of measuring protein. Applicant similarly criticizes Fessler et al. as being limited to a few proteins/RNAs stimulated by LPS and do not address genes in general. Applicant also states that Fessler et al. use an insensitive method of measuring proteins. This has been fully considered but is not

found to be persuasive. Both Lian et al. and Fessler et al. do not limit their conclusions as being limited to the cell types studied, but rather extend their observations to mammalian cells in general. See also Greenbaum et al. (2003, Genome Biology 4:117.1-117.8), who caution against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and

degradation have to be better understood. Thus, the literature shows that those skilled in the art would not assume that increased mRNA levels are predictive of increased protein levels.

Applicant refers to the Polakis declaration, indicating that office personnel must accept an opinion from a qualified expert. Applicant argues that the examiner's suggestion that Dr. Polakis might be misrepresenting the experimental results out of an interest in the outcome of the case is inappropriate. However, the examiner has never stated or implied that Dr. Polakis has *misinterpreted* results. This is not at all the position of the examiner. The previous office action merely discussed issues that case law has indicated are important in the consideration of expert opinion declarations, since it is not true that expert opinion declarations *must* be found persuasive in *all* situations. In assessing the weight to be given expert testimony, the examiner may *properly* consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is

important to note that the instant specification only discloses gene amplification data for PRO351 (i.e., data regarding amplification of PRO351 genomic DNA), and does not disclose any information regarding PRO351 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., and Greenbaum et al. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. This is **not** to imply that Dr. Polakis is misinterpreting any data. (4) Finally, Dr. Polakis refers to facts; however, the data are not included in the declaration so that the examiner could independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

In view of the preponderance of the totality of the evidence, the rejections should be maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number

is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER